AUSTRALIA

Patents Act 1990

IN THE MATTER OF
US Patent Application No.
09/446,109 by The
University of Queensland

STATUTORY DECLARATION UNDER RULE 132

I, Dr Stephen Maxwell Taylor of 17 Perdita Street, Bellbird Park, in the State of Queensland 4300, Commonwealth of Australia, do solemnly and sincerely declare as follows:

1. I am an Associate Professor in the Department of Physiology and Pharmacology at The University of Queensland. I am also an inventor in respect of United States Patent Application No. 09/446,109.

2. My relevant experience is attached hereto as Appendix A. A copy of my curriculum vitae is now shown to me, and is annexed hereto as Exhibit SMT-1.

3. I have read and understood the Office Action dated 18 December 2003 issued in respect of this application.

4. In this Office Action, the Examiner has raised an objection under Section 112 first paragraph that the specification does not provide an enabling disclosure in respect of a method of treating an inflammatory condition, included a method of treating inflammatory arthritis, comprising the step of administering an effective amount of a compound of the invention to a mammal in need thereof. I understand that the Examiner

has formed this opinion on the basis that while the specification discloses certain experimental models, and refers to treatment of rheumatoid arthritis. The Examiner does not consider that these model systems would be regarded in the art as being reasonably predictive of efficacy in other inflammatory arthritides, or in inflammatory conditions other than inflammatory arthritis.

5. I believe that the Examiner is incorrect in taking this position, because I consider that in fact the model systems described in the specification are very well accepted as being generally predictive of anti-inflammatory efficacy, not only in the treatment of rheumatoid arthritis but in other inflammatory conditions. Moreover, I consider that efficacy in the treatment of rheumatoid arthritis is regarded as being reasonably predictive of efficacy in other inflammatory arthritides. I do not consider that any further inventive effort would be required in order to demonstrate efficacy of the compounds of the invention in such conditions.

6. In fact, my colleagues and I have carried out further experimentation using assays and model systems which are well-known in the art, and have not required any further inventive effort in order to do so. This is discussed further below.

7. Using *in vitro* assays, such as those described on page 26, lines 1 to 19, and line 21 to page 27, line 2 of the specification, and the rat carrageenin paw oedema model and rat adjuvant arthritis model described in Example 8 of the specification, we have also demonstrated that the compounds of the invention have anti-inflammatory and anti-arthritic activity. The data obtained using the antigen-induced arthritis model have already been provided to the Examiner in manuscript form with our first response dated 21 April 2000. These results have now been published in *Arthritis and Rheumatism* 2002 46:2476-2485. A copy of this paper is now shown to me and annexed hereto as Exhibit SMT-2.

8. I consider that it is self-evident that it is standard practice in the art to use the cheapest and simplest experimental model first, and to progress a candidate agent to more complex, expensive and time consuming models only if the preliminary screening tests are successful. Both carrageenin-induced inflammation and antigen-induced

arthritis are often thought to be more successful in the rabbit than in the rat, but the rat is a much cheaper animal to use. Antigen-induced arthritis requires prior sensitization, and thus is more time-consuming than carrageenin-induced inflammation. Collagen-induced arthritis is also a notoriously variable model of human rheumatoid arthritis, and expression of the disease is highly variable in rodents, which are the preferred species. Practitioners in the art emphasise the difficulty of using commercial supplies of the antigen, which is associated with poor expression of the disease, and recommend the raising and purifying of collagen antigen from cultured bovine nasal epithelia in the investigators' own laboratory. This increases the costs and expertise required, and so restricts the use of this model. Carrageenin-induced footpad oedema is quick and easy to induce, and can readily be induced in rats; thus it is often used in preliminary screening.

9. The specification of the present application discloses *in vitro* assays for testing candidate anti-inflammatory agents for activity using a suitable surrogate marker. For example, a receptor-binding assay is described at page 26 lines 1 to 19 of the present specification, and an enzyme assay is described at page 26 line 21 to page 27 line 2.

10. I consider that it is a matter of routine then to proceed to *in vivo* assays such as the carrageenin paw oedema and adjuvant arthritis models described at page 27 line 4 to page 28 line 34 of the specification. Similarly, I consider that because the antigen-induced arthritis model is so well known it would require no further inventive activity to test the candidate agent in this model.

11. I emphasise that the *in vitro* assays described in the specification and the rat paw oedema model are general models useful for testing anti-inflammatory activity, and are not restricted to assessment of efficacy in the treatment of arthritis. They are therefore useful as preliminary tests for efficacy in *any* inflammatory condition.

12. The antigen-induced arthritis model shares many histological similarities with human rheumatoid, as well as with other arthritides, including hyperplasia of the synovial membrane, mononuclear cell infiltration, acute and chronic phases, pannus formation, and secondary cartliage erosion. The model also shares the joint swelling and correlated mobility impairment seen in acutely inflamed human arthritic joints. Because

of the antigen-antibody nature of disease induction, the model has also been proposed as a model of reactive arthritis. The immuno-inflammatory basis of the pathology in the antigen-induced arthritis model also mimics several features of human inflammatory arthrides, including synovial and systemic elevations in inflammatory cytokines, and the necessity for immune and inflammatory cell involvement.

13. The antigen-induced arthritis model also shows numerous clinical and pathological similarities with psoriatic arthritis and reactive arthritis, and consequently is considered in the art to be a valid and useful animal model of human inflammatory arthritis. Thus, these features of antigen-induced arthritis in various experimental animals make this model useful as a model for ascertaining the effectiveness of new disease therapies.

14. The antigen-induced arthritis model is a well-established experimental model of arthritis. The model is also highly responsive to anti-inflammatory and immune-based therapies, with significant efficacy shown by ibuprofen, indomethacin, prednisolone, infliximab, leflunomide, methotrexate, and several other agents which are used with success in treating human RA and other arthritides. Copies of these articles are now shown to me, and are annexed hereto as Exhibits SMT-3, SMT-4 and SMT-5.

15. For example, psoriatic arthritis is an inflammatory disease which affects joints, ligaments, tendons and sometimes the spine. Although psoriatic arthritis is associated with psoriasis, and occurs in a subset of patients with psoriasis, these two conditions are considered to be distinct diseases, which may have different pathophysiologies. According to the American College of Rheumatology, non-steroidal anti-inflammatory drugs (NSAIDs) are the initial treatment for arthritis symptoms in patients with psoriatic arthritis, an inflammatory arthritis. Consequently screening methods suitable for testing of anti-inflammatory drugs such as NSAIDs are suitable for testing candidate agents for treatment of this condition. Ankylosing spondylitis is a form of chronic inflammatory arthritis which most often affects the spine, and is treated in the same way as rheumatoid arthritis, with the same armory of drugs, including NSAIDs; Inflixamal (Remicade™), an antagonist of tumour necrosis factor (TNF), a general

mediator of inflammatory responses, is approved for use in the treatment of rheumatoid arthritis. Psoriatic arthritis and ankylosing spondylitis are sometimes referred to as spondyloarthropathies, because they affect areas around the joint where ligaments and tendons attach to bone (enthesitis) rather than the lining of the joint (synovium). However, the underlying pathological mechanisms are thought to be similar.

16. I therefore believe that a person of ordinary skill in the art would, once in possession of the present specification, have a reasonable expectation that the compounds of the invention would be useful in the treatment of numerous inflammatory conditions, especially several inflammatory arthritides, and most notably rheumatoid arthritis. Moreover, such a person would readily be able to test the compounds of the invention in well-established experimental models, without the need to exercise any further inventive effort. Accordingly, the specification provides sufficient support for claims that a method of treating inflammatory arthritis, comprising the step of administering an effective amount of a compound of the invention to a mammal in need thereof.

17. These tests are well known to have broad application. Although the present specification specifically describes the application of the invention to rheumatoid arthritis, a person skilled in the art would clearly understand that the invention has application to inflammatory and arthritic conditions in general, as well as inflammatory arthritic conditions, such as rheumatoid arthritis.

18. We have carried out further experiments using the antigen-induced arthritis model in a study of the role of the complement system in rheumatoid arthritis. The results of these experiments have been set out in a draft manuscript, a copy of which is now shown to me, and is annexed hereto as Exhibit SMT-6.

19. This manuscript describes antigen-induced arthritis as being an established model of RA that involves stimulation of T-lymphocyte reactivity against the immunizing antigen. This model is induced by the immunization of animals with a protein antigen (methylated bovine serum albumin, ovalbumin or fibrin) and an adjuvant, followed by the intra-articular injection of the same antigen. This results in an immune-complex mediated inflammatory response, characterised by chronic synovitis, which is

localised to the injected joint. The ability to localise inflammation to the antigen-injected joint only (monoarticular arthritis) allows for an internal control in the contra-lateral joint. Many of the disease pathologies in this model mimic those seen in human rheumatoid arthritis (Table 1), having both acute and chronic phases of disease. There is also the capacity to induce subsequent flare-ups, which are commonly seen in rheumatoid arthritis, through the re-injection of the antigen.

20. Moreover, the US Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) provides guidance for industry on "Clinical Development Programs for Drugs, Devices and Biological Products for the Treatment of Rheumatoid Arthritis (RA)" on its website at http://www.fda.gov/cber/gdlns/rheumclin.htm. This is an extremely detailed set of guidelines, and Section III at page 6 sets out considerations in rheumatoid arthritis product development, including the selection of appropriate *in vitro* models (animal or human services) and *in vivo* animal models for screening potentially active agents. Page 8 states that collagen-induced arthritis is often considered to be a suitable model; this is a form of antigen-induced arthritis. The rat carrageenin-induced acute model of inflammation is stated to be useful in assessing anti-inflammatory activity, and it is also stated that most of the animal models which involve inflammation in the paw may be used for measuring antiphlogistic (i.e. anti-inflammatory) action of a drug. This is the carageenin-induced footpad inflammation model which is described in the present specification. Copies of the relevant pages from the US Food and Drug Administration's Center for Biologics Evaluation and Research website are now shown to me, and are annexed hereto as Exhibit SMT-7.

21. A cursory search of the PubMed database reveals 25 pages of titles of publications on carrageenin-induced arthritis, and 138 pages of titles of publications on antigen-induced arthritis. Clearly these are both extremely widely-used models.

22. Once the anti-inflammatory and anti-arthritic activity of the compounds of the invention had been demonstrated as described in the present specification, it was a matter of mere routine trial and error experimentation to formulate a method of treating

inflammatory arthritis using the compounds of the present invention, and to test this method using well-accepted animal models, as discussed above. These *in vivo* experiments showed that the method was indeed effective.

23. In fact the results were so favourable that the lead compound of the invention has progressed to human clinical trials in the treatment of rheumatoid arthritis, using oral administration, and of psoriasis, using topical administration. The results of these trials have been favourable, and a summary is now shown to me and is annexed hereto as SMT-8. Please note that this information is to be treated as commercial-in-confidence.

24. I therefore consider that a person of ordinary skill in the art would, once in possession of the present specification, have a reasonable expectation that the compounds of the invention would be useful in the treatment of numerous inflammatory conditions, especially several inflammatory arthritides, and most notably rheumatoid arthritis. Moreover, such a person would readily be able to test efficacy of the compounds of the invention for this purpose in well-established experimental models, without the need to exercise any further inventive effort. Accordingly, I consider that the specification provides an enabling disclosure of a method of treating inflammatory arthritis, comprising the step of administering an effective amount of a compound of the invention to a mammal in need thereof.

And I make this solemn Declaration by virtue of the Statutory Declarations Act 1959, and subject to the penalties provided by the Act for the making of false statements in Statutory Declarations, conscientiously believing the statements contained in this Declaration to be true in every particular.

DECLARED at Brisbane this 12 day of MAY 2004

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Stephen Maxwell Taylor

Before me: .....

A person empowered to witness Statutory Declarations under the laws of the State of Queensland, Commonwealth of Australia